REMARKS AND AMENDMENTS

I. THE AMENDMENTS

Please amend Claims 15, 17, 29 31 and 47. Support for the amended claims can be found at least as follows:

Claim 15 - Support for Claim 15 can be found at least in Example 10 and Example 11, page 73-74 of the specification.

Claim 17 - Support for Claim 17 can be found at least in Example 10 and Example 11, page 73-74 of the specification.

Claim 29 - Support for Claim 29 can be found at least on page 2, lines 13-14 of the specification.

Claim 47 - Support for Claim 47 can be found at least in Example 10 and Example 11, page 73-74 of the specification.

II. THE REJECTIONS

A. The Rejection under 35 U.S.C. § 101

Claims 15-17, 19, 20, 27-31 and 47 stand rejected as allegedly not being supported by a specific and substantial asserted utility or a well established utility based on an in vitro assay. Applicants respectfully traverse the rejection.

The legal standard with respect to *in vitro* or animal model data providing pharmacological activity has been commented on in *Cross v. Iizuka*, 753 F.2nd 1040,1051 224 USPQ 739 747-48 (Fed Cir. 1985)

> "We perceive no insurmountable difficulty, under appropriate circumstances, in finding that the first link in the screening chain, *in vitro* testing, may establish a practical utility for the compound in question. Successful *in vitro* testing will marshal resources and direct the expenditure of effort to further in vivo testing of the most potent compounds, thereby providing an immediate benefit to the public, analogous to the benefit provided by the showing of an *in vivo* utility."

Furthermore, from the MPEP 2107.03 (III)

"If reasonably correlated to the particular therapeutic or pharmacological utility, data generated using *in vitro* assays, or from testing in an animal model or a combination thereof almost invariably will be sufficient to establish therapeutic or pharmacological utility for a compound, composition or process."

The legal standard accepts that *in vitro* or animal model data is acceptable utility as long as the data is "reasonably correlated" to the pharmacological utility described. Furthermore, Hudziak et al., found that tumor-derived breast cancer cell lines overexpressing the HER2/c-erbB-2 gene product could be growth arrested by a monoclonal antibody (Hudziak et al., Mol Cell Biol (1989) 9(3):1165-1172). This early in vitro data was sufficient enough to proceed with this monoclonal antibody into clinical trials, issuance of a U.S. patent (U.S.S.N. 5,677,171) and a successful FDA approved drug, HERCEPTIN™ .

The mixed lymphocyte reaction (MLR) is a well-established *in vitro* assay for assessing the ability of a test compound to stimulate T cell proliferation. MLR has been extensively used and is considered to be the best *in vitro* model available to study graft-versus-host disease and graft rejection. It is well known that the transplantation of tissues or organs between individuals with MHC incompatibilities quickly activates the recipient's immune system which then attempts to destroy the transplanted tissue or organ. Transplantation across minor histocompatibility loci generally induces a more indolent response. Physicians analyze the major and minor histocompatibility differences to predict the success of the graft and to adjust the aggressiveness of immunosuppressive therapy. Inhibitors of MLR find utility in suppressing unwanted immune response, which might, for example, result in graft rejection. For example, the ability of tepoalin, an immunomodulatory compound, to suppress graft-versus-host reaction, has been demonstrated in a MLR assay (Fung-Leung *et al., Transplantation* 60:362-8 (1995)).

The MLR assay has also been used to identify immunostimulators, which find utility, for example, in diseases where the T cell activation is desirable, such as various types of cancers (see, e.g. Harrison *et al., Blood* 97:2764-71 (2001)), or in the case of patients whose immune system has been compromised. Thus, it has been shown that patients with AIDS-related complex demonstrate impaired autologous mixed lymphocyte reaction (Garbrecht *et al., Clin. Exp. Immunol.* 67:245-51 (1987)).

The MLR assay is described in standard textbooks, including, for example, *Current Protocols in Immunology*, unit 3.12; edited by J E Coligan, A M Kruisbeek, D H Marglies, E M Shevach, W Strober,

National Institutes of Health, published by John Wiley & Sons, Inc., which is referenced in EXAMPLE 10, the entire content of which is expressly incorporated by reference into the disclosure of the present application. In brief, in this method cell proliferation is assayed by mixing isolated T cells and then adding the test compound, (specifically Bolekine in this example), in different concentrations. The experiment is controlled by the addition of CD4-IgG which does not cause proliferation, and media without Bolekine protein. The experiment is done in triplicate with two different concentrations of the Bolekine test protein. The effect the of Bolekine protein on proliferation is monitored quantitatively by following the incorporation of tritiated thymidine. The assay is simply a measure of immune cell proliferation in response to a test compound. Bolekine protein added to the media in the nanomolar range (12.40 to 124.00 nM) as shown in Table 7 of the specification on page 74, stimulates proliferation over control by 112% and 192.7% for the respective concentrations. A sequence analysis of the Bolekine protein determines that Bolekine is a member of the CXC family of chemokines, containing the 4 canonical cysteines, and was cloned using probes based on the MIP-2 chemokine (see all of Example 1, beginning at page 65). Chemokines are known in the literature for stimulating leukocyte movement, stimulating proliferation and activation of different immune cell types (Baggiolini et al., (1997) Annu. Rev. Immunol. 15:675-705).

The Examiner has rejected the claims solely on the alleged basis that the in vitro MLR assay is an in vitro assay, and is not predictive of the immune response in general. The Examiner describes several valid points about the MLR assay, but does not dispute that it is an widely used and reliable assay, and that it can produce valid data. The Applicant submit that in this instance, the MLR assay is used to examine only immune cell proliferation and this is reflected in the claims.

The Examiner has not taken into consideration that the Skin Vascular Permeability assay is an *in vivo* assay, demonstrating another trait of the chemokine family, that of chemotaxis. Inflammatory cells migrate to the site of injection as evaluated by sectioning the skin and histological examination.

Based on the *in vitro* MLR assay, the *in vivo* Skin Vascular Permeability Assay, and the structure of Bolekine as a CXC chemokine, there is proof that Bolekine is a chemoattractant and stimulator of immune cells, consistent with the characteristics of the chemokine family. Also, Applicants submit the *in vitro* and animal model data provided within the specification is "reasonably correlated" utility within the scope of the claims as defined by the legal standard. Therefore, given the whole of the scientific

evidence, and the application fo the legal standard for utility, the Applicants respectfully submit the rejection be withdrawn.

In light of the above amendments and remarks, Applicants believe that this application is now in condition for immediate allowance and respectfully request that this case pass to issue.

The examiner is invited to contact the undersigned at (650) 225-3733 if any issues may be resolved in that manner.

Respectfully submitted,
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